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Original Article

Repurposing Efavirenz for Anticancer Therapy with Curcumin Combination in Solid Lipid Nanoparticle Formulation

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ABSTRACT

Background: The aim of this study was to explore the potential of repurposing the anti-HIV drug Efavirenz (EFZ) in combination with Curcumin (CUR) for cancer therapy. EFZ is an antiviral drug and selective anti-HIV drug through its Non-Nucleoside Reverse Transcriptase Inhibition (NNRTI) mechanism. The poor survival rate of many cancers has been investigated by new and alternative therapies against immortal tumors. Repurposing is the best option because it minimizes the drug development timeline and avoids phase 1 trials. **Materials and Methods:** The selected drugs were formulated as Solid Lipid Nanoparticles (SLNPs) via hot emulsification to enhance solubility. All the evaluated parameters for the characterization of SLNPs were within the acceptable limit. **Results:** Scanning electron microscopy images and nanosize of the drugs were further confirmed by -38.6 mV and 0.204 of zeta potential and polydispersity index values. SLNPs sustained the liberation of the drug for about 24 hr and the pattern of drug release followed Higuchi kinetics. CUR and EFZ combination produced significant growth arrest in MCF-7 breast cell line formulations compared to individual EFZ, CUR formulations. The combined formulation showed a significant loss of viability: only 11.63% of cell viability, CUR 13.61% of viability and EFZ 15.98% of cell viability were retained. **Conclusion:** The cytotoxic activity of the combined EFZ and CUR formulation was potentiated. Treatment of HIV-1-positive patients with combined EFZ and CUR formulations with different modes of action might reduce the incidence of breast cancer with fewer side effects.

Keywords: Repurposing, Efavirenz, Curcumin, Solid lipid nanoparticles, Anticancer activity, Breast cancer cells.

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INTRODUCTION

Carcinoma is a dominant factor in global mortality rates, with a reported mortality rate of $1.0x10^7$ deaths in 2020.[1] 30% of cancer cases are reported every year in underdeveloped and developing countries due to the lack of early diagnosis facilities, the last stage presentation. Usage of tobacco, alcohol consumption, unhealthy diet, lack of physical fitness exercises and polluted surroundings are known threats to cancer.[2] The cancer deaths in 2020 were lung cancer ($1.8x10^6$ deaths), colorectal cancer ($9.4x10^5$ deaths), hepatocellular cancer ($8.3x10^5$ deaths), gastric cancer ($7.69x10^5$ deaths); and breast ($6.85x10^5$ deaths). Carcinogenic infections caused by different bacterial and viral organisms accounted for 13% of cancers in 2018.[3] Oncogenic viruses elevate the threat of liver and cervical cancer. The influence of HIV on the life-span of women with breast cancer was evaluated by Sadigh's *et al*., (2019). The team investigated increased breast cancer mortality in women positive with HIV compared to those without HIV.[3] This study demonstrated the need for drug therapy that can treat multiple life-threatening infections. Efavirenz is a marketed first-line antiretroviral drug used in the treatment of AIDS.[4] The cytotoxic activity of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) such as Efavirenz (EFZ), Rilpivirine (RPV), Etravirine (ETR) and Lersivirine was investigated for anticancer activity.[5] The growing resistance exhibited by cancer cells necessitates the exploration of new drug combinations that can mitigate cancer risks through innovative drug delivery mechanisms like nanosponges, nanoparticles, emulgels and transdermal drug delivery systems. These advancements aim to augment drug delivery efficiency while concurrently decreasing potential toxicity to adjacent healthy cells.[6] Extensive investigations are underway regarding the potential of natural products as anticancer agents. However, the outcomes of these studies often fall short of expectations in terms of their effectiveness. This has prompted researchers to explore innovative approaches to augmenting

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the anticancer activity of these natural compounds.[7,8] One such strategy involves the synergistic combination of natural drugs with synthetic formulations. By merging the inherent advantages of natural products with the precision and customization offered by synthetic compounds, researchers aim to create novel therapeutic agents that exhibit enhanced anticancer properties. This cross-disciplinary approach has the potential to reveal new avenues for cancer treatment and underscores the ongoing efforts to bridge the gap between the potential of natural products and their practical application in the fight against cancer. With this reasoning, the current study aimed to repurpose EFZ against cancer in combination with CUR. CUR exhibits distinctive anticancer activity by inhibiting different cellular signaling pathways.[9] The current research focused on utilizing the lipid-soluble property of the selected drugs to make a combined formulation that could increase its solubility and dissolution rate thereby resulting in enhanced anticancer activity in AIDS patients. The SLNP formulation is such a unique formulation that might be appropriate for the selected drugs. Further, the nanoformulation was characterized and its anticancer activity on MCF-7 cells was studied.

MATERIALS AND METHODS

Materials

Aurobindo Pharma Limited provided Efavirenz as a gift. Glyceryl Monostearate (GMS), curcumin, cholesterol, stearic acid and Tween 80 were procured from HiMedia Laboratories Pvt. Ltd., Mumbai, India. MCF-7 Breast Cancer Cell Lines (MCF-BCCL), Dulbecco`s Modified Eagle Media (DMEM) with low glucose (Gibco, Invitrogen), Fetal Bovine Serum (FBS) (Gibco, Invitrogen) Antibiotic-Antimycotic 100X solution (Thermofisher Scientific).

Methods

Studies on saturation solubility

The selection of lipids is the most pivotal step in the fabrication of SLNPs. Saturation solubility studies were performed by dissolving EFZ in different lipids like stearic acid, cholesterol and Glyceryl Monostearate (GMS), in varying concentrations from 0.5 to 1.5 g of lipid with 0.5 g of drug. The melted lipid was added to an ample portion of the drug and the solution was dissolved. The drug was added steadily until the solution became clear and pale. The resultant mixture was then prepared by dissolving in methanol and passing through a membrane filter with a pore size of 0.22 µm. The drug content in the filtrate was measured using a UV-vis spectrophotometer at 247 nm. Similarly, the saturation solubility of CUR was determined and the absorbance was determined at 425 nm. The drug's solubility was calculated as

$$\text{Solubility of the drug} = \frac{\text{Absorbance in lipid} \times \text{Concentration}}{\text{Absorbance from standard curve}} \times \text{Dil. factor}$$

Preparation of EFZ and CUR SLNPs

EFZ- and CUR-loaded SLNs were fabricated by a slightly modified hot shear homogenization technique followed by ultrasonication.[10] EFZ, CUR and GMS were solvated in a methanol and chloroform (1:1) mixture. The entire organic solvent content was drawn out using a rotary flash evaporator. The fixed organic layer melted by heating it to a temperature 5°C higher than its melting point. Stabilizer-tween 80 was dissolved in distilled water to create the aqueous phase, which was then heated to the same temperature as the oil phase. Under homogenization, conditions were maintained for 30 min with a homoginizer (Remi-RQ129-D, Byahut Scientico Jaipur, India) and the heated water phase was introduced into the oil phase at 2500 rpm and 70°C. The attained coarse oil in water emulsion was agitated using a probe sonicator (ULTRA-PS-20-125, India) for 25 min. EFZ and CUR stacked SLNPs were obtained by cooling the hot nano-emulsion to room temperature and were then preserved at 4°C. The compositions of the various SLNPs are presented in Table 1.

Drug-excipient interaction study

With a mortar and pestle, 1:300 parts of the drug and KBr were triturated together. The pellet was prepared from the triturated mixture under 1000 kg/cm^2 compression. Then, the pallet was scanned using FTIR spectrometer (FTIR Spectrometer Alpha Bruker India Scientific Pvt Ltd., Mumbai, India). The IR spectra of the drug, drug with other excipient blends were evaluated.[11]

Characterization of SLNPs

SLNP surface morphology

The finest characteristics of the SLNPs were evaluated using Scanning Electron Microscopy (SEM3200, CIQTEK products, Japan).

Polydispersity Index (PDI) and Zeta Potential (ZP)

PDI measures the wideness of the molecular weight distribution of the fabricated nanoparticles. The particle distribution was estimated by using dynamic light scattering (Zeta sizer Ver 6.20, MAL 1004428) and the effective surface charge and its stability were determined in terms of zeta potential.

Differential scanning calorimetric studies

The physical and chemical transitions of the developed SLNPs and pure drugs were evaluated using a DSC thermogram (DSC-60, Shimadzu Corporation, Japan) for pure and combined drug formulations.

Drug entrapment efficiency

A specified volume of SLNPs (10 mL) was vortexed at 18000 rotation cycles per min for 30 min at 20°C (Remi, R-8C). The drug concentration was estimated in the supernatant by separating the

lipid content. The efficiency of drug entrapment in SLNPs was determined.[12]

$$\% \text{ of entrapped drug} = \frac{\text{DWNP}}{\text{TWNP}} \times 100$$

DWNP-Drug weight in SLNPs

TWNPs-Theoretical weight of drug-loaded in SLNPs

Drug release studies

Drug release investigations were conducted using the dialysis bag method. With a molecular cutoff value of 14 kDa, the dialysis sac releases the free drug into dissolution medium and retains the SLNPs. Double distilled water was used to equilibrate the bag for 12 hr before use. The SLNP formulation (2 mL) was kept in the bag and the openings of the bag were sealed. The samples containing bags were saturated in 50 mL phosphate buffer (pH 7.4) containing a conical flask and then rotated on an orbital shaker that was regulated thermostatically at 37°C±0.5°C at 140 rpm. Samples were collected at predetermined intervals and a new buffer was used to restore the volume.[13,14] Each sample was determined by the spectroscopic method after passing through a 0.22 μm membrane filter.

Stability studies

The stability of the formulated SLNPs was determined by following the standard protocol.[15]

Drug release kinetics

The aggregate measures of EFZ and CUR discharge from the SLNPs at various spans were fitted with kinetic models to identify the drug release mechanism.

Determination of anticancer activity by MTT assay

The 96-well microplate was seeded with cells preserved overnight at 37°C, 95% humidity and 5% CO_2. Different amounts (400, 200, 100, 50, 25, 12.5 µg/mL) were used to treat the cells. The cells were treated for 48 hr and incubated with cisplatin as a control. After two washes with Phosphate Buffer Solution (PBS), 20 µL staining solution (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) was added to each well and the mixture was then incubated at 37°C. The formazan crystals were dissolved in 100 µL of DMSO after 4 hr. At 570 nm, the color intensity of each concentration was predicted.[16]

$$\% \text{ of the cells survived} = \frac{\text{Avg OD of the compound}}{\text{Avg OD of negative control}} \times 100$$

The IC_{50} of compounds was calculated by graph Pad Prism Version 5.1.

RESULTS

Among the screened lipids, GMS was chosen as the lipid for SLNPs fabrication based on its solubility values. EFZ and CUR have 0.4899±0.031 g/g and 0.4657±0.421 g/g solubility in GMS. The medium-chain length of GMS may be the reason for the enhanced solubility of selected drugs compared with other lipids.

Compatibility studies

FTIR spectroscopy confirmed the compatibility of the drug with excipients. All the primary chemical groups associated with EFZ, CUR and SLNPs combined formulations (Figures 1(a-c)) remained persistent or showed slight changes in the peaks identified. The dipole moment in the molecules is responsible for this change.

Characterization of SLNPs

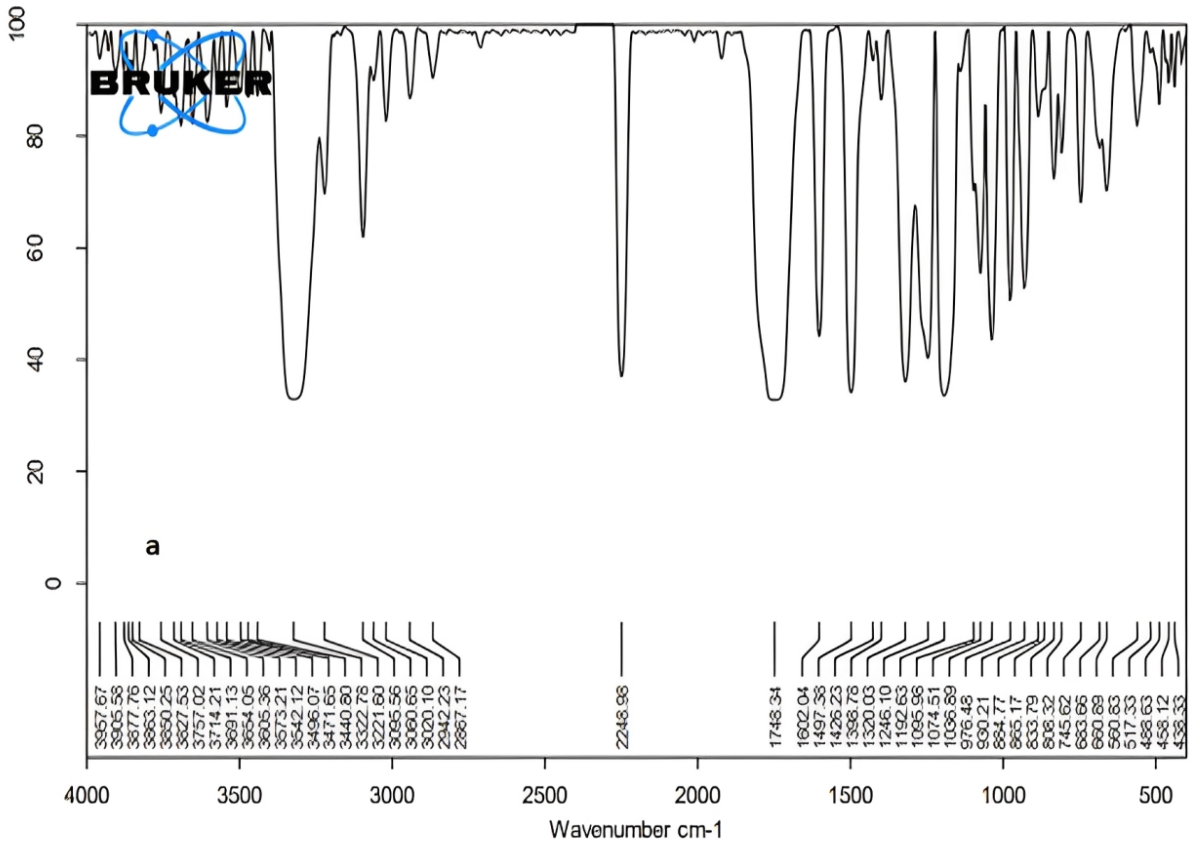
All formulations exhibited entrapment efficiency (%) in the range of 70.31% to 79.23% from F1-F6. Among all the formulations, F6 exhibited good entrapment efficiency with a GMS concentration of 1.5 g and tween-80 concentration of 2%. EFZ and CUR exhibited 78.23±0.52, 79.23±0.23 of entrapment efficiency respectively. When the lipid concentration increases, there is an improvement in the entrapment efficiency that is comparable to that reported by Abdelbary *et al.*[17] The smooth surfaces containing the spherical shapes of the SLNPs were confirmed by SEM images as shown in Figure 2.

From the endothermic peak, it was evident that EFZ had a melting point of 139.1°C and for CUR of 177.8°C (Figures 3 (a-c). The endothermic peak of SLNPs did not significantly change. The melting points obtained in the combined formulation almost coincided with the melting points of the pure drugs, indicating

Table 1: Formulation of SLNPs.

Formulations	F1	F2	F3	F4	F5	F6
EFZ (mg)	500	-	250	500	-	250
CUR (mg)	-	500	250	-	500	250
GMS (g)	1.0	1.0	1.0	1.5	1.5	1.5
Tween 80 (% w/v)	2	2	2	2	2	2
Methanol (mL)	50	50	50	50	50	50
Chloroform (mL)	50	50	50	50	50	50
Distilled water (mL)	10	10	10	10	10	10

EFZ-Efavirenz, CUR-Curcumin, GMS-Glyceryl monostearate.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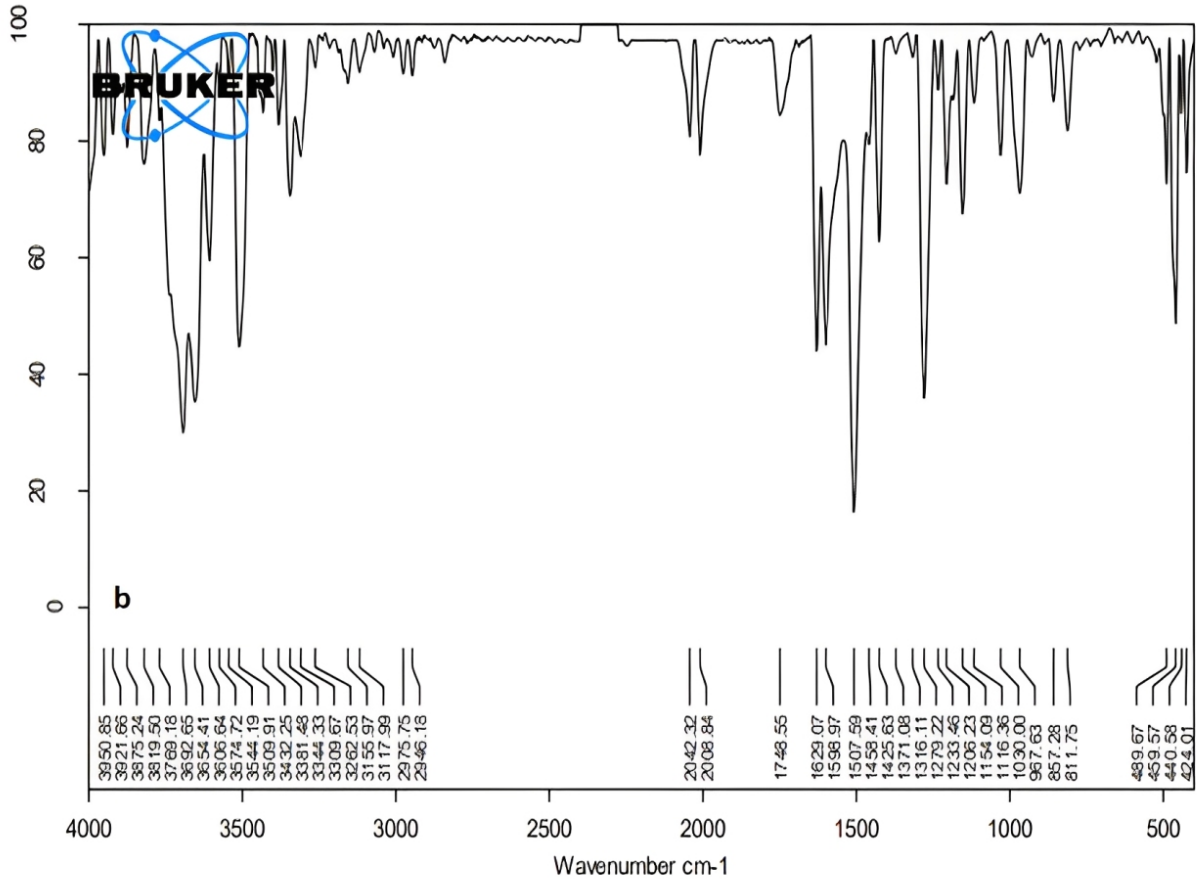
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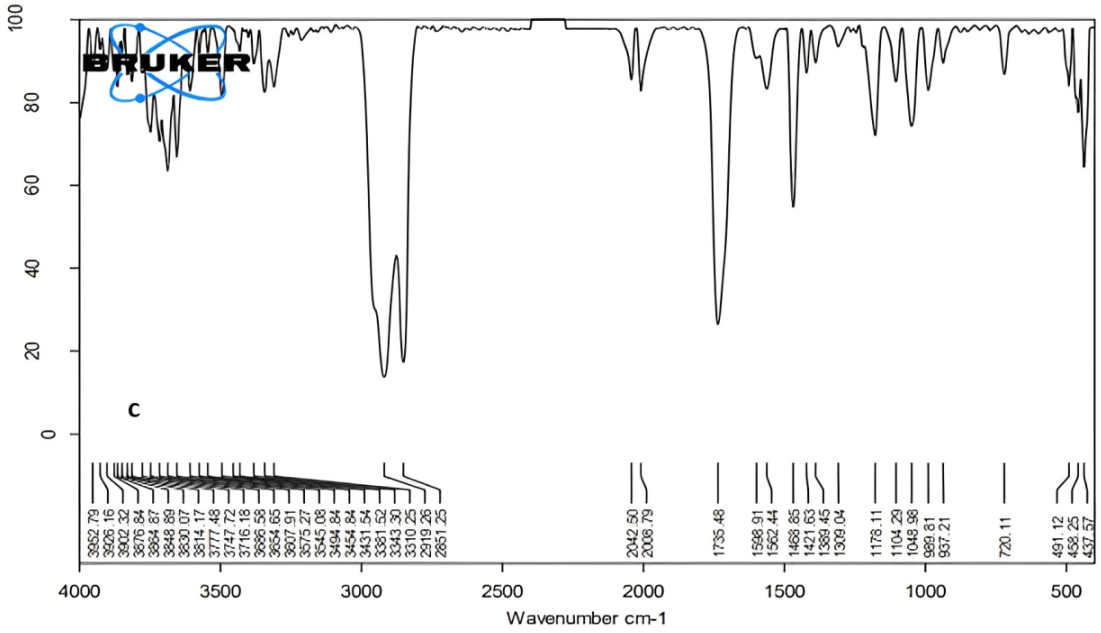

Figure 1: FTIR of Efavirenz (a), Curcumin (b), optimized formulation F6 (c).

that the encapsulated drugs did not crystallize in SLNPs blend. Finally, the thermal behaviour of the encapsulated drugs was not altered by the lipid system used for encapsulation.

ZP and PDI were found to be -38.6 mV and 0.204 respectively, for the optimized (F6) formulation, as shown in Figures 4(a-b). This indicates that the prepared SLNPs have sufficient surface charge to prevent aggregation of the vesicles and are more stable.

The *in vitro* drug release profiles of the EFZ and CUR loaded SLNs formulations ranged from 11.24 to 94.23%. Within 24 hr, 94% of the drug was discharged (Table 2).

In vitro kinetic analysis

The drug release data were fitted into several kinetic models. With an R^2 value of 0.9805 for EFZ and 0.9742 for CUR, the optimized formulation F6 confirmed that the active ingredient was released according to zero-order kinetics. The Higuchi and Peppas plots provided additional confirmation of the drug release mechanism: n=0.45 indicates Case I or Fickian diffusion; 0.45<n<0.89 indicates aberrant behavior, or non-Fickian transport; n=0.89 indicates Case II transport; and n>0.89 indicates Super Case II transport. The optimized formulation (F6) had 'n' values of 0.553 and 0.5674, which indicates transport that is not Fickian (Table 3).

Stability studies

The quality of the SLNPs was confirmed by conducting stability testing. All the prepared formulations were stable under different temperatures and humidity conditions.

Anti-cancer activity in cell lines

The cytotoxic activity of the EFZ, CUR, EFZ and CUR SLNPs combination was evaluated on MCF-BCCL at an IC_{50} value of 80.53 µg/mL for EFZ and 47.84 µg/mL for the combined formulation (Table 4). The CUR and EFZ combination in SLNPs produced significant growth arrest in MCF-BCCL compared with individual formulations. In this study, the effects of CUR and EFZ from 12.5 µg/mL-400 µg/mL on MCF-7 cell morphology were tested. After 60 hr, the combined Formulation (F6) treated cell lines showed remarkable cell shrinkage, rounding and limited separation from other cells, supporting the cytotoxic effect of curcumin on MCF-6 cells (Figures 5 (a-b)). Upon determining the impact of SLNPs formulation on cell viability using the MTT assay, it was confirmed that a decrease in cell viability at a concentration of 400 µg/mL in combined formulation showed a significant loss of viability with 11.63% of cell viability, whereas with CUR 13.61% of viability and with 15.98% of cell viability was retained with EFZ. Compared with the individual formulations, the combined formulations showed the highest anti-cancer activity.

DISCUSSION

The low expenditure of money and time on drug development is the main advantage of drug repurposing. A large number of drugs are in the pipeline of major pharmaceutical companies and they are adopting this method. The global drug repurposing market value is predicted to reach USD 30920 million by 2027, from USD 24570 million in 2020, to a CAGR of 2.9% during 2021-2027.[18]

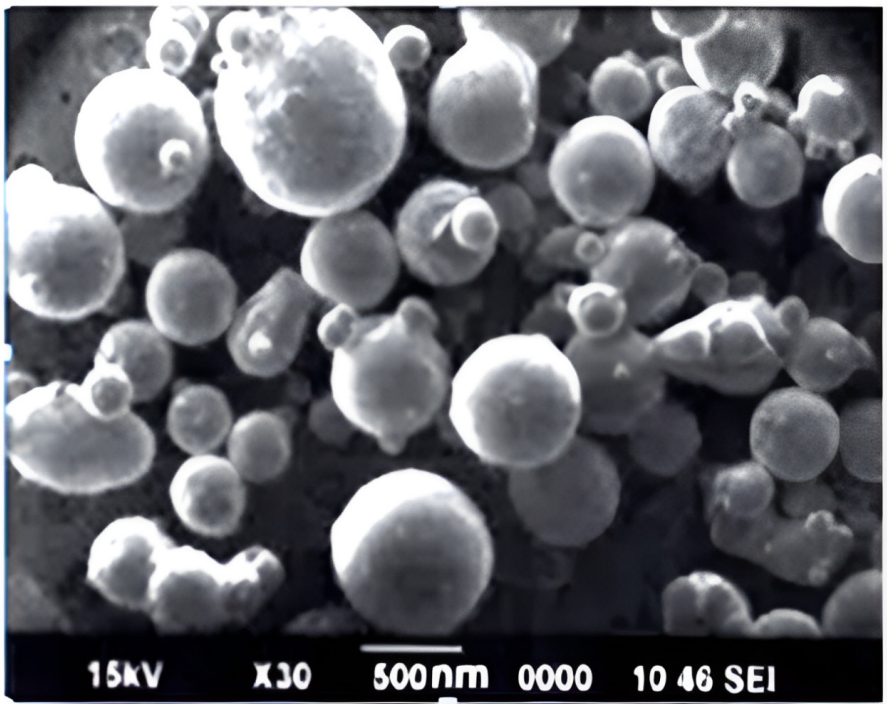

Figure 2: SEM image of SLNPs.

Table 2: ***In vitro*** **diffusion of EFZ and CUR loaded SLNPs.**

Time (hr)	F1		F2		F3		F4	
	EFV	CUR	EFV	CUR	EFV	CUR	EFV	CUR
0	0	0	0	0	0	0	0	0
0.5	17.01	16.63	13.06	15.68	14.18	17.36	11.24	13.36
1	18.63	17.98	14.20	16.13	16.02	18.23	17.8	15.23
2	19.38	18.23	15.14	18.17	18.10	19.31	18.06	19.31
3	20.06	19.25	17.28	20.80	20.32	21.63	20.1	21.63
4	22.30	22.36	21.91	23.93	22.62	23.42	22.83	23.42
6	32.82	31.68	27.68	30.45	31.11	31.63	31.02	32.63
8	36.01	37.36	32.16	35.36	47.18	34.86	40.06	37.86
12	56.80	58.02	56.23	58.20	59.20	59.83	53.86	52.83
24	75.23	77.07	78.02	77.36	89.02	90.86	94.23	93.86

Most drug development studies aim to explore the unidentified pharmacological activities of existing drugs. Worldwide, more than 2000 drugs have approved, with an average of more than six appropriate targets[19-21] that could be beneficial for offering a keen, peculiar, secure and reasonably economical therapy. Considering these findings, there is a need to develop the most suitable formulation to achieve cancer targets in the host with minimal side effects. In light of this, the current investigation sought to repurpose the anti-HIV drug EFZ for anticancer activity with a CUR combination. EFZ has been previously used as a proven anticancer drug in various cancers[22,23] owing to its selective toxicity against cancer cells.[24] The solubility of the selected drugs in lipids required the development of SLNPs via hot shear homogenization. The selection of different excipients, such as lipids and surfactants, was based on preliminary testing procedures. The compatibility between EFZ and CUR was confirmed by FTIR studies.[5] The compatibility of EFZ and CUR in their nanoform was confirmed by FTIR data, as most characteristic bands were still preserved (Figure 1). In SLNPs, the major functional groups associated with EFZ, GMS and CUR did not change. The dipole moment observed in the molecules may be the cause of the slight shift in the peaks. The FTIR spectroscopy findings indicated that many drugs might be contained within the lipid carrier. The improved solubility and drug dissolution rate were achieved with the F6 formulation because the increased concentration of GMS from 1 to 2 g improved the hydrophobic environment which aided in

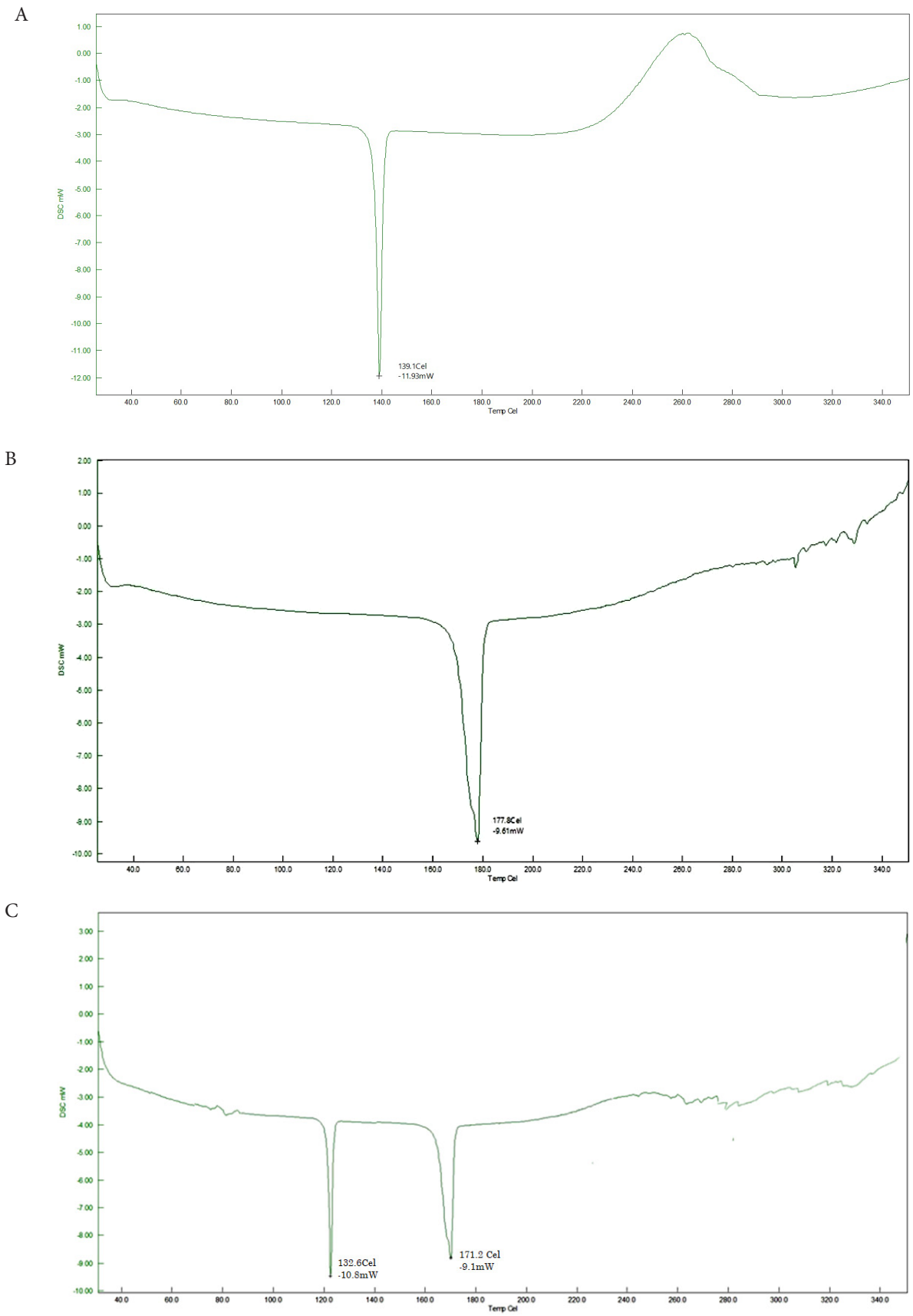

Figure 3: DSC of EFZ (a), CUR (b), EFZ+CUR (c).

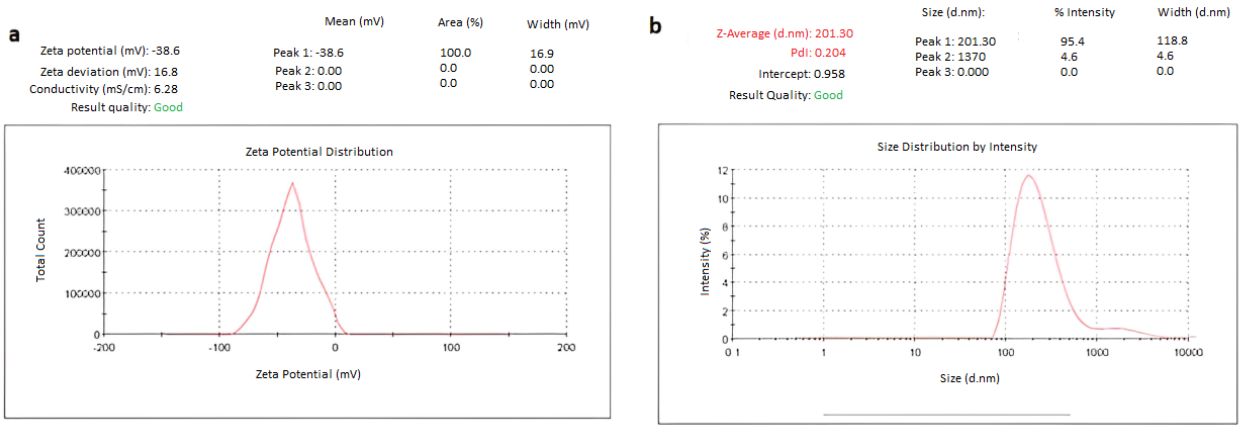

Figure 4: Zeta-potential (a), Polydispersity index (b), of F6 formulation.

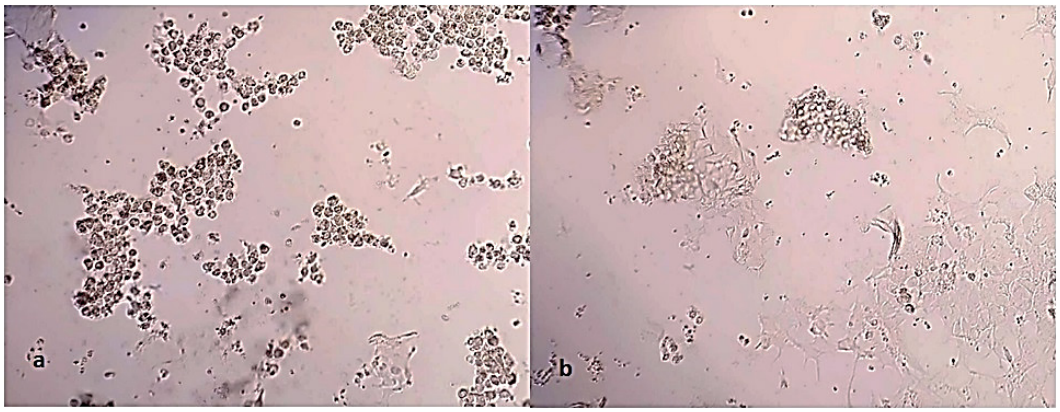

Figure 5: (a) Anticancer activity on MCF-7 cell lines by EFZ-SLNPs, (b) EFZ and CUR-SLNPs.

Table 3: R^2 **Values of Formulation F6.**

R2 Values of Formulation F6		
	Efavirenz	**Curcumin**
Zero Order	0.9905	0.9742
First Order	0.8706	0.8675
Higuchi	0.9905	0.9417
Korsemeyer peppas	0.489	0.5002
n value	0.553	0.5674

the enhanced solubility of hydrophobic drugs such as EFZ and CUR. The lipid matrix formed by GMS also facilitated controlled drug release, which improved the overall dissolution rate of the encapsulated drugs.[25] The initial drug release was slow because of the lesser mobility of the drug within the solid phase of the lipid. The current formulation caused mild drug expulsion to the outer surface of the nanoparticles, resulting in mild burst release and leakage of the drug in a controlled manner. Compared with the other kinetics, the optimized formulation exhibited more linearity in the Higuchi model of release kinetics. The "n" value under the Korsmeyer-Peppas model was close to 0.5, indicating that the SLN formulation adheres to Fickian diffusion.[26] Furthermore, the study showed cooperativity in the encapsulation of drug combinations via synergistic action at molar equivalence.

Acquiring quick resistance to multiple antiviral drugs in HIV-1 demands a different combination of drugs with multi-targeting capabilities. CUR and EFZ are such a combination that exhibits unique antiviral and anticancer activities through apoptosis and inhibiting proliferation of the virus, invading cancers through the inhibition of many Intracellular signaling cascades.[27] With non-nucleoside reverse transcriptase inhibitors mechanism, EFZ is used in cancer treatment. The different mechanisms of the two-drug combinations potentiated the anticancer activity against breast cancer cell lines even at reduced concentrations. At 100 µg/mL concentration, EFZ retained 46.4% and CUR retained 46.09% of cell viability, the combination of drugs (concentration reduced to half) retained 23.7% of cell viability. The synergistic activity of the selected drug combination might be the best choice

Table 4: % of cell viability retained after treating with SLNPs.

	% of cell viability of MCF-7					
Concentration (µg/mL)	EFZ		CUR		EFZ and CUR	
400	15.98	18.88	13.61	15.76	11.63	13.39
200	28.01	27.59	26.17	24.32	20.95	22.41
100	45.64	47.15	43.32	48.86	23.44	23.86
50	65.35	65.56	58.21	53.34	34.02	34.65
25	72.2	74.27	67.45	69.81	79.46	80.71
12.5	79.67	81.33	76.38	74.42	93.78	89.63
Negative Control	100					

for patients with HIV and can help to reduce the occurrence of breast cancer without the development of drug resistance and side effects.

CONCLUSION

The solubility of SLNPs increased and exhibited more than 85% drug release. The cytotoxic activity was potentiated by combining CUR. It can be speculated that in HIV-1 positive patients, taking EFZ drugs might help to reduce the incidence of breast cancer. EFZ and CUR combination with a different mechanism of action (a synthetic drug with a natural active ingredient) might be a new option in the treatment of breast cancer with fewer side effects.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

EFZ: Efavirenz; **CUR:** Curcumin; **HIV:** Human immunovirus; **NNRTI:** Non-nucleoside reverse transcriptase inhibition; **SLNPs:** Solid lipid nanoparticles; **AIDS:** Acquired immuno deficiency syndrome; **MCF-7:** Michigan Cancer Foundation-7; **MTT:** 3-(4,5-Dimethyl thiazol-2-yl)-2,5-diphenyltetrazolium bromide.

SUMMARY

The successful development of EFZ and CUR-loaded solid lipid nanoparticles was accomplished by hot homogenization. GMS and Tween 80 were selected as the primary lipid component and surfactant, respectively. *In vitro* drug release studies have indicated that all SLN formulations exhibit regulated drug release, with F6 emerging as the preferred formulation. The diverse mechanisms of the two-drug combinations enhanced the anticancer efficacy against breast cancer cell lines even at low concentrations. At a concentration of 100 µg/mL, EFZ maintained 46.4% cell viability, whereas CUR maintained 46.09% cell viability. However, the combination of drugs (concentration halved) retained only 23.7% cell viability. The synergistic effect of the selected drug combination in F6 could be an optimal option for the patients with HIV, potentially reducing the incidence of breast cancer without fostering drug resistance or adverse effects.

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